

shRNA-mediated decreases in c-Met levels affect the differentiation potential of human mesenchymal stem cells and reduce their capacity for tissue repair.

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Public Summary:

In these studies we examined the effects of reducing the receptor c-met on the surface of human bone marrow-derived mesenchymal stem cells. The reduction was accomplished by using inhibitory RNA (RNAi, shRNA) technology. It was learned that this receptor is important on the surface of the primitive MSCs that traffic to areas of injury and initiate revascularization and tissue repair. These studies formed the early basis on which we began the CIRM-funded studies, through learning the techniques of genetically engineering the MSCs to produce robust amounts of small interfering RNA (siRNA). Although the work was not specifically funded by CIRM, it is highly related and Dr. Nolte was a CIRM-funded investigator during the completion of these studies. Manuscript acknowledgements state: "We would like to thank the California Institute for Regenerative Medicine (CIRM) for funding a continuation of the work to study MSC engineered to produce and deliver siRNA (CIRM TR1-01257: [Nolte])."

Scientific Abstract:

Mesenchymal stem cells/marrow stromal cells (MSC) are adult multipotent cells that can augment tissue repair. We previously demonstrated that culturing MSC in hypoxic conditions causes upregulation of the hepatocyte growth factor (HGF) receptor c-Met, allowing them to respond more robustly to HGF. MSC preconditioned in hypoxic environments contributed to restoration of blood flow after an ischemic injury more rapidly than MSC cultured in normoxic conditions. We now investigated the specific role of HGF/c-Met signaling in MSC function. An shRNA-mediated knockdown (KD) of c-Met in MSC did not alter their phenotypic profile, proliferation, or viability in vitro. However, we determined that while HGF/c-Met signaling does not play a role in the adipogenic differentiation of the cells, the disruption of this signaling pathway inhibited the ability of MSC to differentiate into the osteogenic and chondrogenic lineages. We next assessed the impact of c-Met KD on human MSC function in a xenogeneic hindlimb ischemia injury model. A 70% KD of c-Met in MSC resulted in a significant decrease in their capacity to regenerate blood flow to the ischemic limb, as compared to the MSC transduced with control shRNA. MSC with only a 60% KD of c-Met exhibited an intermediate capacity to restore blood flow, suggesting that MSC function is sensitive to the dosage of c-Met signaling. The current study highlights the significance of HGF/c-Met signaling in the capacity of MSC to restore blood flow after an ischemic injury and in their ability to differentiate into the osteogenic and chondrogenic lineages.

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